

Struma Ovarii: Histopathological Mimics, Immunohistochemical Clues, and Diagnostic Pitfalls

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Abstract

Struma ovarii is defined as a monodermal teratoma comprising chiefly thyroid tissue and accounts for approximately 1% of all ovarian tumors. Its histology is highly variable. Cystic, microfollicular, trabecular, oxyphilic, clear-cell, and solid patterns can closely imitate surface epithelial, sex cord-stromal, neuroendocrine, and metastatic tumors, and most misdiagnoses stem from failure to consider struma rather than from its rarity. The reverse is also important: proliferative but benign struma is commonly overdiagnosed as carcinoma, while highly differentiated follicular carcinoma of ovarian origin (HDFCO), a histologically bland struma, is underrecognized, although it tends to spread beyond the ovary. This narrative review organizes the mimics of struma ovarii by histological pattern and summarizes the morphological and immunohistochemical discriminators that resolve them, including thyroglobulin, thyroid transcription factor-1 (TTF-1), paired box gene 8 (PAX8), inhibin, steroidogenic factor-1 (SF-1), forkhead box L2 (FOXL2), and neuroendocrine markers. It also touches upon the principal diagnostic pitfalls: benign struma versus malignant struma, HDFCO, and the so-called peritoneal strumosis, strumal carcinoid, and metastatic cervical thyroid carcinoma, along with frozen-section errors. It summarizes recent molecular data on struma-derived carcinomas, such as B-Raf proto-oncogene, serine/threonine kinase (BRAF), rat sarcoma virus (RAS), and telomerase reverse transcriptase (TERT) promoter alterations, with emphasis on their exploratory nature. A stepwise diagnostic algorithm and a reporting checklist are also proposed

Categories: Obstetrics/Gynecology, Pathology, Oncology

Keywords: differential diagnosis, highly differentiated follicular carcinoma, immunohistochemistry, monodermal teratoma, ovarian tumor, strumal carcinoid, struma ovarii, thyroid-type carcinoma

Introduction And Background

The diagnosis of struma ovarii is made when thyroid tissue constitutes >50% of a teratoma or when a smaller thyroid component forms a nodule that is grossly recognizable [1,2]. Ovarian tumors of this type make up approximately 1% of cases and typically occur in individuals in their 50s and 60s and are almost always unilateral [1-3]. Recent studies have shown that the diagnosis of these tumors can rarely be made before surgery. In a study performed on 170 Korean patients, struma-derived carcinoma was found in 15 of 170 (8.8%) patients. However, none of these patients were detected via preoperative computed tomography or magnetic resonance imaging [3]. Similarly, in a Chinese study involving 103 patients, preoperative ultrasonography identified struma ovarii in only two out of 98 women; most lesions were cystic or mainly cystic and were often categorized as Ovarian-Adnexal Reporting and Data System (O-RADS) category 4 or 5 [4]. A 2025 study of 40 patients also found that 22 of 40 (55%) tumors were purely cystic on ultrasonography [5]. In a recent multicenter study, clinical features such as ascites, pleural effusion (pseudo-Meigs syndrome), and raised levels of cancer antigen 125 (CA-125) were seen in one-third of patients, further mimicking epithelial ovarian carcinoma [6]. Consequently, the diagnosis is primarily based on histopathological examination.

The World Health Organization's (WHO) classification of female genital tumors, fifth edition, classifies struma ovarii under monodermal teratomas and acknowledges various related entities, as outlined in Table 1 [1]. Roth and Talerman pointed out that the term "malignant struma ovarii" has been broadly employed for true thyroid-type carcinoma, strumal carcinoid, and peritoneal implants of benign thyroid tissue, recommending more accurate terminology [2]. The concept of highly differentiated follicular carcinoma of ovarian origin (HDFCO), proposed by Roth and Karseladze and subsequently refined, acknowledges that struma, which is benign on histopathology, can still exhibit malignant behavior [7,8]. In contrast, strumal carcinoid is a unique combination of thyroid follicles and carcinoid tissue [9]. This review adopts this terminology, concentrating on the histological mimics of struma ovarii, the immunohistochemical and molecular indicators that differentiate them, and the errors leading to misdiagnosis, while incorporating recent cohort and molecular studies.

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Entity	Definition	Key point for the pathologist
Benign struma ovarii	Thyroid tissue forming >50% of a teratoma, or a grossly visible thyroid nodule; normal, hyperplastic, adenomatous, or thyroiditic [1,2]	May be cellular and proliferative; this alone does not indicate malignancy [1,2,5]
Struma-derived thyroid-type carcinoma	Papillary, follicular, oncocytic, or (rarely) poorly differentiated, high-grade, or anaplastic carcinoma arising in struma [1,3,6]	Apply thyroid criteria; avoid the vague term "malignant struma ovarii" [1,2]
HDFCO	Histologically bland thyroid tissue that has spread beyond the ovary [1,7,8]	Diagnosed by extra-ovarian spread, not by ovarian histology; may present decades after oophorectomy [7,8]
Strumal carcinoid	Intimate admixture of thyroid follicles and carcinoid, usually trabecular [1,9]	Historically mislabeled as malignant struma; behaves as a low-grade neuroendocrine tumor [2,9]
Peritoneal strumosis	Older term for peritoneal implants of bland thyroid tissue[7,8]	Now largely subsumed under HDFCO; does not imply benign behavior [1,7,8]

TABLE 1: Struma ovarii and related entities in the WHO classification

HDFCO: highly differentiated follicular carcinoma of ovarian origin; WHO: World Health Organization.

Struma can be mistaken for other ovarian tumors due to two main factors. Firstly, the thyroid follicular epithelium can exhibit growth patterns such as microfollicular, solid, trabecular, cystic, oxyphil, and clear-cell, which are similar to sex cord-stromal, neuroendocrine, and epithelial tumors. Secondly, the presence of thyroid tissue in the ovary is unexpected, especially when no other teratomatous components are identified. Another challenge is the frequent discrepancy between histological malignancy and biological behavior in struma. Many tumors that fulfill the histological criteria for thyroid carcinoma remain localized to the ovary and are resolved through surgery. In contrast, HDFCO is a form of struma that appears completely benign under microscopic examination but can spread beyond the ovary to the peritoneum or distant locations, sometimes years later [7,8]. Numerous reviews in the literature focus on clinical management, with few providing a practical, pattern-based guide for pathologists that integrates morphology, immunohistochemistry, molecular data, and these behavioral contradictions. This review, therefore, aims to (i) outline the morphological mimics of struma ovarii and methods to differentiate them, (ii) establish the criteria distinguishing benign struma, struma-derived carcinoma, and HDFCO, and (iii) summarize the current immunohistochemical, molecular, and prognostic evidence, along with its limitations. It uses WHO terminology and includes cohort and molecular studies published between 2024 and 2026.

Review
Literature search strategy

This narrative review was based on a structured search of PubMed/MEDLINE and Google Scholar, focusing on articles published from the inception of the databases up to September 2026, with particular attention to works from 2020 onwards. The search strategy employed a combination of terms such as "struma ovarii", "malignant struma ovarii", "struma-derived carcinoma", "thyroid-type carcinoma AND ovary", "highly differentiated follicular carcinoma", "peritoneal strumosis", "strumal carcinoid", "immunohistochemistry", "BRAF", "RAS", "TERT", "frozen section", and "differential diagnosis", utilizing the Boolean operators AND and OR. Additionally, reference lists from the retrieved articles were reviewed. We included original studies in English (cohorts, case series, and immunohistochemical or molecular studies), systematic reviews, meta-analyses, registry analyses, and the current WHO classification. Isolated case reports were considered only if they presented a unique diagnostic feature not found elsewhere. Titles and abstracts were screened, and potentially relevant articles were fully reviewed by both authors independently, resolving disagreements through discussion. Classical morphological studies were included if they remained the primary source for a diagnostic criterion. The findings were synthesized qualitatively. In cases of conflicting studies, preference was given to larger series, studies with extended follow-up, and WHO criteria, while distinguishing individual study results from those of systematic reviews and meta-analyses. As the goal was to provide a practical diagnostic synthesis rather than a quantitative answer to a single question, and given the variability in study design and outcome definitions, a narrative approach was selected: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 reporting, applicable to systematic reviews, was not followed, and no pooled estimates were calculated. No formal risk-of-bias assessment was conducted. Most of the evidence available comes from small retrospective series with variations in patient populations, histological classification, follow-up duration, and treatment, and these limitations should be considered when interpreting the data summarized below.

Gross features

Grossly, struma classically appears as a solid, glistening, brown-green, or amber gelatinous mass that may replace the ovary or form a nodule within the wall of a mature cystic teratoma [1,2]. However, many tumors are predominantly cystic. Szyfelbein et al. described 20 cystic strumae in which large cysts lined by flattened epithelium obscured the thyroid nature of the lesion [10], and recent series continue to report cystic or multilocular architecture as the dominant gross and imaging pattern [5,11]. As diagnostic thyroid tissue might be confined to solid areas or septa, it is crucial to thoroughly sample solid nodules, cyst septa, dermoid walls, and any hemorrhagic or fleshy regions.

Microscopic patterns

Microscopically, struma recapitulates the full spectrum of cervical thyroid histology and adds several patterns that are uncommon in the neck [12]. The most recognizable pattern features normofollicular and macrofollicular tissue, where follicles of different sizes are bordered by cells ranging from flattened to cuboidal, possessing round, evenly distributed nuclei, and are filled with dense eosinophilic colloid. If there is shrinkage in the follicles and lack of colloid, or if the cellular proliferation is in the form of solid sheets, the tumor may imitate an adult granulosa cell tumor or another type of sex cord-stromal tumor. The arrangements of follicular cells in forms such as trabecular, insular, and pseudotubular can show resemblance to carcinoid or Sertoli cell tumors, whereas collapsed follicles might mimic endometrioid glands [12].

Cytological variants and proliferative changes

Cytological variations introduce additional complexity. Oxyphil (Hürthle) cells are characterized by abundant granular eosinophilic cytoplasm, the presence of which suggests the potential for a hepatoid neoplasm or a steroid cell tumor. In contrast, cytoplasmic clearing or vacuolation results in clear-cell and signet-ring appearances, which are reminiscent of clear cell carcinoma or Krukenberg tumors [12]. Non-neoplastic and proliferative changes seen in cervical thyroid (e.g., papillary hyperplasia, adenomatous nodules, and lymphocytic thyroiditis) are also observed in struma. In a study involving 54 proliferative and histologically malignant strumae, Devaney et al. observed that neither marked cellularity nor proliferative architecture alone was indicative of malignant behavior [13]. Among all patterns, the three features that are indicative of struma include dense eosinophilic colloid with scalloping or retraction artifact, birefringent calcium oxalate crystals within colloid when seen under polarized light, and residual teratomatous elements found elsewhere in the specimen [2,12].

Histopathological mimics

Struma is commonly missed when sections show dominant non-classic patterns. In a study by Szyfelbein et al., 30 cases of struma were initially misdiagnosed as other types of ovarian tumors, such as sex cord-stromal tumors, carcinoid, and epithelial neoplasms [12]. Table 2 lists each histopathological pattern along with its principal mimics and outlines the morphological and immunohistochemical features that help in distinguishing them. When it comes to identification of granulosa and Sertoli cell tumors, among the sex cord-stromal markers, steroidogenic factor-1 (SF-1) and forkhead box L2 (FOXL2) are highly sensitive immunohistochemical markers and outperform traditional markers like inhibin and calretinin [14,15]. Neuroendocrine differentiation in both strumal carcinoid and primary ovarian carcinoid can be effectively demonstrated by synaptophysin and chromogranin [16,17], while clear cell carcinoma can be demonstrated by napsin A [18]. Among several patterns of struma, thyroglobulin and thyroid transcription factor-1 (TTF-1) remain the most reliable positive markers. The sensitivity and specificity data for SF-1, FOXL2, and napsin A, however, come from studies of sex cord-stromal tumors and clear cell carcinoma rather than of struma itself [14,15,18]; their use in excluding struma is therefore extrapolated and is most informative alongside thyroglobulin and TTF-1 staining. Representative examples are shown in Figure 1.

Struma pattern	Main mimics	Favors struma	Favors mimic	Useful immunohistochemical markers	References
Microfollicular/solid	Adult and juvenile granulosa cell tumor	True colloid, oxalate crystals, round nuclei without grooves, teratomatous elements	Grooved nuclei, Call-Exner bodies, luteinized theca cells	Tg, TTF-1, PAX8 in struma; inhibin, calretinin, SF-1, FOXL2 in GCT	[12,14,15]
Trabecular/insular/tubular	Sertoli or Sertoli-Leydig cell tumor; carcinosarcoma	Colloid in at least some lumens	Leydig cells, retiform areas; salt-and-pepper chromatin	Inhibin, SF-1 (Sertoli); chromogranin, synaptophysin (carcinosarcoma); Tg (struma)	[12,14,16,17]
Struma with trabecular endocrine cells	Strumal carcinosarcoma	Uniform follicular cells only	Second neuroendocrine population merging with follicles	Synaptophysin, chromogranin on trabecular cells; Tg on both components	[9,16,17]
Cystic	Serous or mucinous cystadenoma; simple or follicle cyst	Follicles in septa, colloid-like content, eosinophilic cuboidal lining	Ciliated or mucinous columnar lining	Tg and TTF-1 on flattened lining	[5,10,11]
Oxyphil	Steroid cell tumor; hepatoid yolk sac tumor; metastatic RCC or HCC	Follicular architecture, colloid	Lipid-rich cells, Reinke crystals; Schiller-Duval bodies	Inhibin, melan-A (steroid); AFP, SALL4, glypican-3 (YST); Tg (struma)	[1,12]
Clear-cell/signet-ring	Clear cell carcinoma; metastatic RCC; Krukenberg tumor	Bland nuclei, colloid, thyroid markers	Hobnail cells, hyaline globules; mucin-containing signet cells	Napsin A, HNF-1 β (CCC); CK20, CDX2, SATB2 (GI); Tg (struma)	[1,12,18]
Glandular/pseudotubular	Endometrioid adenofibroma or carcinoma	Colloid; no squamous morules or endometriosis	Columnar cells, squamous morules	ER, PR (endometrioid); Tg (PAX8 is shared)	[1,12]
Papillary hyperplasia	Serous borderline tumor; papillary thyroid carcinoma	Papillae with colloid, no PTC-type nuclei	Hierarchical branching (SBT); clearing, grooves, inclusions (PTC)	WT1 (SBT); CK19, HBME-1, galectin-3 supportive only	[1,13]

TABLE 2: Histological patterns of struma ovarii, their mimics, and discriminating features

Tg: thyroglobulin; TTF-1: thyroid transcription factor-1; PAX8: paired box gene 8; GCT: granulosa cell tumor; SF-1: steroidogenic factor-1; FOXL2: forkhead box L2; RCC: renal cell carcinoma; HCC: hepatocellular carcinoma; AFP: alpha-fetoprotein; SALL4: spalt-like transcription factor 4; YST: yolk sac tumor; CCC: clear cell carcinoma; HNF-1 β : hepatocyte nuclear factor-1 beta; CK: cytokeratin; CDX2: caudal-type homeobox 2; SATB2: special AT-rich sequence-binding protein 2; GI: gastrointestinal; ER/PR: estrogen/progesterone receptor; SBT: serous borderline tumor; PTC: papillary thyroid carcinoma; WT1: Wilms tumor 1; HBME-1: Hecate Battifora mesothelial-1.

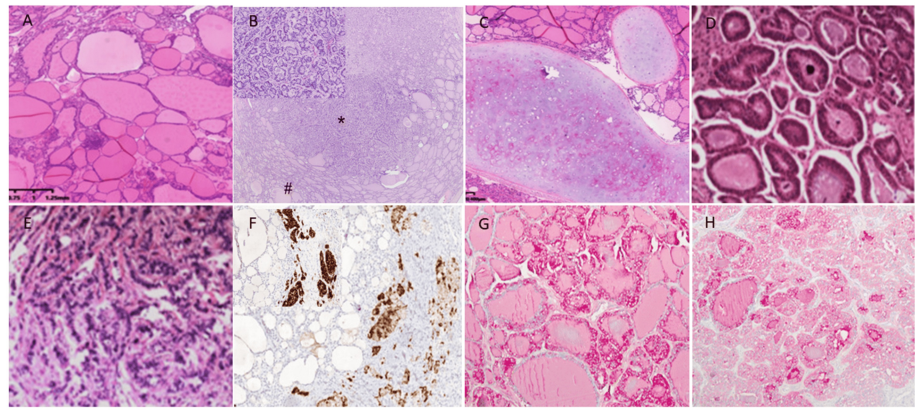


FIGURE 1: Histopathological and immunohistochemical features of struma ovarii and its principal mimics

(A) Pure struma ovarii composed of thyroid follicles of varying size (H&E, $\times 40$). (B) Strumal carcinoid with two components: neoplastic thyroid-type follicles (#) intermixed with a neuroendocrine component (*) of monomorphic round nuclei in trabecular and rosette-like arrangements (H&E; scale bar, 500 μ m) and inset, higher magnification of the neuroendocrine component. (C) Struma ovarii with a mature teratoma component (H&E, $\times 40$). (D) Insular carcinoid tumor (H&E, $\times 100$). (E) Trabecular carcinoid tumor, a mimic of trabecular struma (H&E, $\times 100$). (F) Chromogranin A expression in strumal carcinoid; inset, synaptophysin ($\times 100$). (G, H) Thyroglobulin expression in the follicular component (G) and in the neuroendocrine-like component (H) of strumal carcinoid ($\times 100$). Panels A, C and F are reproduced from Chen et al. [5]; panels B, G and H from Theurer et al. [16]; and panels D and E from Dai et al. [17]. All are published under the Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>). Panels were cropped, resized and relabeled. H&E: hematoxylin and eosin; Tg: thyroglobulin.

In practice, three confusions account for most errors. Microfollicular or solid struma is separated from adult granulosa cell tumor by its true colloid, round nuclei without grooves, and the absence of Call-Exner bodies, and the distinction is confirmed by thyroglobulin and TTF-1 positivity with SF-1 and FOXL2 negativity [12,14,15]. Trabecular struma differs from carcinoid and Sertoli cell tumor by colloid in at least some lumens and by thyroglobulin expression, whereas a second, synaptophysin-positive population signals strumal carcinoid [12,16,17]. Cystic struma is recognized by searching cyst septa for small groups of follicles and by staining the flattened lining for thyroglobulin [10]. The less common oxyphil, clear-cell, glandular, and papillary patterns are summarized in Table 2.

Diagnostic pitfalls

As outlined in the Introduction, histology and behavior often diverge in struma [2,13,19], so diagnostic errors occur in both directions. Overdiagnosis leads to unnecessary thyroidectomy and radioactive iodine, while underdiagnosis deprives patients of surveillance. The following subsections address the most frequent of these errors.

Overdiagnosis of Proliferative Struma as Carcinoma

In benign struma, histological features such as cellularity, solid growth, microfollicles, mild nuclear enlargement, and mitoses are commonly observed; however, these are not indicative of carcinoma [13]. As there is a lack of a capsule, assessment of capsular invasion, which is important for follicular carcinoma in the neck, is not possible [8]. Therefore, follicular carcinoma should only be diagnosed when there is clear evidence of invasion into the ovarian stroma beyond the struma, vascular invasion, or metastasis. For diagnosing papillary carcinoma, the presence of well-defined nuclear features that are characteristic of papillary thyroid carcinoma is required and not just papillary architecture.

In a blinded review of 86 cases, Shaco-Levy et al. discovered that the degree of papillary or follicular alterations had little correlation with outcomes. However, high-grade nuclei, necrosis, and frequent mitoses were indicators of tumors that recurred [19]. Robboy et al., in their examination of 88 cases, demonstrated that most histologically malignant strumae remained confined to the ovary and did not metastasize [20]. In the context of struma-derived carcinoma, recent studies have used the WHO 2022 classification for thyroid neoplasms. One study based on nine cases, published in 2026, observed several carcinomas, including papillary, follicular, oncocytic, and differentiated high-grade; all tumors were classified under stage I, and post-operatively, all patients were disease-free [21]. Likewise, a Korean study found papillary carcinoma in seven of 15 (46.7%) and follicular carcinoma in four of 15 (26.7%) struma-derived carcinomas, and none of the patients died from the disease [3].

Under-Recognition of HDFCO

HDFCO consists of thyroid tissue that cannot be differentiated from normal thyroid or adenomatous goiter, but it can invade organs that lie close, implant on the peritoneum, or metastasize [7,8]. Diagnosis cannot be made from the ovarian tumor alone. Indicators include disease outside the ovary, attachment to the bowel or pelvic organs, and recurrence, which might occur many years later: Roth and Karseladze reported para-aortic nodal metastasis 26 years post-oophorectomy [7], and Robboy et al. found that 27 out of 88 cases had spread beyond the ovary [20]. In a Korean study, two out of three tumors involving the peritoneum or omentum were thyroid-type tumors with uncertain malignant potential rather than clear carcinomas [3]. Molecular evidence suggests the biologically malignant behavior of these lesions: A recent study published in 2024 found that all strumae showing peritoneal spread at the time of diagnosis or during follow-up had at least one gene alteration [22]. Histopathology reports should mention if the struma is adherent, ruptured, or associated with peritoneal nodules, and long-term follow-up with serum thyroglobulin should be advised.

Peritoneal Strumosis Versus HDFCO

The term "peritoneal strumosis" has traditionally been linked with nonmalignant implants. Nonetheless, due to the risk of these deposits evolving and spreading, the most recent WHO classification categorizes them in the HDFCO group, indicating a low-grade malignant potential [1,7,8]. It is recommended not to use the term strumosis in reports, or if it is mentioned, it should be explicitly stated that it does not imply a benign condition.

Metastatic Cervical Thyroid Carcinoma

Thyroid cancer can mimic struma when it spreads to the ovary. Additionally, carcinoma originating from struma may occur alongside a distinct primary tumor in the neck [23]. In a Korean study, four out of 15 individuals with struma-originating carcinoma underwent thyroidectomy due to thyroid cancer [3]. Factors that suggest metastasis include bilateral or multinodular ovarian deposits, involvement of the surface, absence of teratomatous elements, and an established thyroid primary. In contrast, a dermoid component, a unilateral mass, and normal imaging of the neck suggest an origin in struma. Therefore, neck ultrasonography is recommended in all cases of carcinoma originating from struma. The presence of a shared B-Raf proto-oncogene, serine/threonine kinase (BRAF) V600E mutation does not confirm metastasis, as there have been instances of synchronous independent tumors with matching mutations but differing loss-of-heterozygosity profiles [23].

Strumal Carcinoid Labeled as Malignant Struma

Strumal carcinoid, a combination of thyroid follicles with trabecular or insular carcinoid, was often incorrectly identified as malignant struma in the past [2,9]. In an analysis of 13 cases, thyroglobulin was found in both parts of each tumor, synaptophysin was present in the neuroendocrine part of all cases, the Ki-67 index was < 2% in 12 of 13 tumors, and a 47-gene panel revealed no clinically significant mutations [16]. In a 2025 study of primary ovarian carcinoids, strumal carcinoid was the most prevalent subtype, appearing in nine out of 15 tumors, all of which were stage I, and none of the patients experienced recurrence after a median follow-up of 92.5 months [17]. Similarly, in a 2025 study of 40 strumae, all three tumors labeled as malignant were strumal carcinoids, with no recurrence observed [5]. Identifying the neuroendocrine component is crucial to avoid both overdiagnosing thyroid-type carcinoma and misclassifying it as a metastatic carcinoid tumor.

Frozen Section and Sampling

At intraoperative consultation, microfollicular struma may be misread as granulosa cell tumor, and trabecular struma as Sertoli cell tumor or carcinoid [12]. Struma is rarely suspected before surgery, and cystic architecture, ascites, elevated CA-125, and enhancing solid components often suggest an epithelial malignancy [3-5]. When colloid and teratomatous elements are not evident, definitive classification is best deferred to permanent sections, on which solid nodules should be sampled extensively because a focus of papillary carcinoma may measure only a few millimeters. The morphological checks at frozen section follow the sequence set out in the practical diagnostic approach section.

Prognosis and Management

The outcome is influenced by the histological subtype and, most importantly, the extent of the disease. Benign struma, including its proliferative forms, is resolved through excision and does not require thyroid-specific monitoring [13]. Carcinoma originating from struma that is limited to the ovary typically has a very favorable prognosis: in two recent institutional studies, no patients succumbed to the disease [3,21]. A 2025 systematic review and meta-analysis of 376 patients (95 from case reports and 281 from case series) reported pooled overall survival of 91% at 10 years and 87% at 20 years. Recurrence occurred in 26 of 95 patients (27%) with individual data, at a median of four years, and none of the factors tested, including adjuvant thyroidectomy, radioactive iodine, and hormone suppression, significantly predicted survival.

[24]. For stage I disease, a pooled analysis of 164 published cases indicated that unilateral (hazard ratio 0.36, P = 0.019) and bilateral (hazard ratio 0.19, P = 0.004) salpingo-oophorectomy were associated with a lower risk of recurrence compared to cystectomy [25].

The risk increases with extraovarian spread, high-grade histology, and the HDFCO phenotype, where recurrence may occur decades post-surgery [7,20]. According to national registry data, a high-risk category derived from American Thyroid Association guidelines was linked to decreased overall survival (hazard ratio 4.0, 95% confidence interval (CI) 1.11-14.26, P = 0.034), yet only a small fraction of high-risk patients received radioactive iodine [26]. In clinical practice, conservative surgery accompanied by neck ultrasonography and serum thyroglobulin monitoring is appropriate for low-risk carcinoma confined to the ovary. Total thyroidectomy followed by radioactive iodine is typically reserved for HDFCO, extraovarian or recurrent disease, and high-grade carcinoma, partly to enable thyroglobulin to function as a tumor marker, although a survival advantage has not been proven [24-26]. These recommendations are based on retrospective, registry, and pooled case data with varied treatment and follow-up rather than prospective trials. Therefore, management should be tailored by a multidisciplinary team, and pathology reports should document the subtype, extent, and surface status, which are crucial for risk assessment.

Immunohistochemistry and molecular adjuncts

Immunohistochemistry

Thyroglobulin, in conjunction with TTF-1, confirms thyroid differentiation, whereas PAX8 alone does not, as it is also expressed in Müllerian tumors (Table 3). In a study conducted in 2026, all nine carcinomas originating from struma showed expression of TTF-1, thyroglobulin, and PAX8. The majority also showed positive expression of cytokeratin 19 (CK19), Hector Battifora mesothelial-1 (HBME-1), and galectin-3, with a frequent loss of CD56 [21]. Although these markers are related to papillary carcinoma, they are supportive rather than diagnostic, making nuclear criteria essential. None of these markers distinguishes benign from malignant struma or predicts HDFCO. For indeterminate ovarian tumors, a streamlined first-line panel includes thyroglobulin, TTF-1, inhibin or SF-1 (along with FOXL2 if available), and synaptophysin or chromogranin [14-16].

Marker	Struma ovarii	Main use	Caveat	References
Thyroglobulin	Positive (follicles, colloid)	Most specific thyroid marker	Diffuses into adjacent tissue; interpret cytoplasmic staining	[16,21]
TTF-1	Positive (nuclear)	Thyroid vs. sex cord-stromal and Müllerian tumors	Positive in some endometrioid and other carcinomas	[16,21]
PAX8	Positive	Supports thyroid or Müllerian origin	Does not separate struma from Müllerian epithelium	[1,21]
Inhibin, calretinin, SF-1, FOXL2	Negative	Granulosa, Sertoli, and steroid cell tumors	SF-1 and FOXL2 more sensitive than inhibin; data extrapolated from sex cord-stromal tumor studies	[14,15]
Chromogranin, synaptophysin	Negative (positive in strumal carcinoid)	Carcinoid and strumal carcinoid	Follicular component of strumal carcinoid may co-express chromogranin	[16,17]
CK19, HBME-1, galectin-3, CD56	Variable	Supportive for papillary carcinoma (CD56 loss)	Not diagnostic; rely on nuclear criteria	[21]
BRAF V600E (VE1)	Negative in benign struma	Supports carcinoma	Misses non-V600E variants such as BRAF p.G469A; a negative result does not exclude carcinoma or HDFCO	[21,22]

TABLE 3: Immunohistochemical markers in the evaluation of struma ovarii

TTF-1: thyroid transcription factor-1; PAX8: paired box gene 8; SF-1: steroidogenic factor-1; FOXL2: forkhead box L2; CK19: cytokeratin 19; HBME-1: Hector Battifora mesothelial-1; CD56: neural cell adhesion molecule; BRAF: B-Raf proto-oncogene, serine/threonine kinase; VE1: BRAF V600E-specific monoclonal antibody clone; HDFCO: highly differentiated follicular carcinoma of ovarian origin.

Molecular Findings

Research into molecular characteristics indicates potential genetic differences between benign and

malignant struma, though current evidence remains preliminary. Schmidt et al. identified BRAF mutations in four out of six carcinomas originating from struma, while none were found in nine benign strumae [27]. Additionally, next-generation sequencing revealed activating mutations in neuroblastoma RAS viral oncogene homolog (NRAS), BRAF, or Janus kinase 3 (JAK3) in five of six carcinomas [28]. A 2024 investigation involving 31 strumae showed molecular changes in seven of eight (87.5%) biologically malignant, seven of 10 (70%) histologically malignant, and one of 13 (7.7%) benign tumors. The BRAF p.G469A variant, uncommon in cervical thyroid carcinoma and not detected by the VE1 monoclonal antibody, was the most prevalent alteration, with telomerase reverse transcriptase (TERT) promoter changes appearing solely in biologically malignant cases [22]. A 2026 study reported a rat sarcoma virus (RAS)-like profile in five of eight sequenced carcinomas, with no TERT promoter mutations observed [21]. These findings are derived from small retrospective series ranging from six to 31 cases, employing varied gene panels and limited follow-up, and are not included in WHO diagnostic criteria [1]. Consequently, a BRAF or RAS mutation might support a carcinoma diagnosis in morphologically borderline lesions, and a TERT promoter mutation could warrant increased monitoring. However, no single alteration confirms malignancy independently, and a negative result does not rule out HDFCO. Diagnosis remains reliant on morphological assessment and disease extent.

Practical diagnostic approach

Figure 2 summarizes the stepwise approach for any ovarian tumor containing follicles, trabeculae, cysts, or oxyphil or clear cells of uncertain nature. The clinical and operative context, including imaging, CA-125, a history of thyroid cancer, and intraoperative adhesion, rupture, or peritoneal nodules, should be known before the slides are interpreted. Initially, thyroid differentiation is determined by detecting colloid, calcium oxalate crystals, and teratomatous components, along with verifying the expression of thyroglobulin and TTF-1 against a panel that includes inhibin or SF-1 and a neuroendocrine marker [1,12,14]. Subsequently, the presence of a clear-cut trabecular or insular neuroendocrine population is assessed. If such a population is found, a diagnosis of strumal carcinoid is made, which is then confirmed using synaptophysin and chromogranin [16,17].

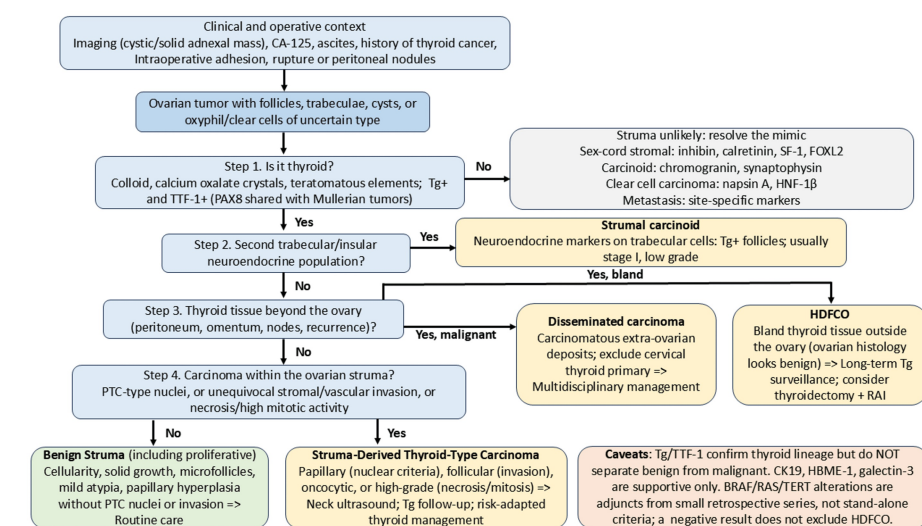


FIGURE 2: Stepwise diagnostic approach to an ovarian tumor with suspected thyroid differentiation

The algorithm begins with the clinical and operative context and proceeds through four histological questions. Benign (including proliferative) struma, struma-derived thyroid-type carcinoma, and highly differentiated follicular carcinoma of ovarian origin (HDFCO) are shown as separate endpoints, each with its defining criteria and management implications. The caveat box summarizes the limitations of immunohistochemical and molecular markers. CA-125: cancer antigen 125; Tg: thyroglobulin; TTF-1: thyroid transcription factor-1; PAX8: paired box gene 8; SF-1: steroidogenic factor-1; FOXL2: forkhead box L2; HNF-1β: hepatocyte nuclear factor-1 beta; HDFCO: highly differentiated follicular carcinoma of ovarian origin; PTC: papillary thyroid carcinoma; RAI: radioactive iodine; CK19: cytokeratin 19; HBME-1: Hecton Battifora mesothelial-1; BRAF: B-Raf proto-oncogene, serine/threonine kinase; RAS: rat sarcoma virus; TERT: telomerase reverse transcriptase. This figure was created by the authors on the basis of references [1-3,7,8,12-28].

In the third step, it is necessary to evaluate the presence of thyroid tissue beyond the ovary. The presence of histologically bland thyroid tissue outside the ovary suggests HDFCO rather than benign strumosis, whereas carcinomatous deposits indicate disseminated struma-derived carcinoma. Irrespective of the findings, it is important to rule out primary cervical thyroid carcinoma with the help of neck ultrasonography, particularly if the ovarian condition is bilateral, affects the surface, or lacks teratomatous components [7,8,23]. For tumors confined to the ovary, the final step involves applying thyroid criteria: papillary carcinoma is

identified by well-developed nuclear characteristics, follicular carcinoma by clear stromal or vascular invasion, and high-grade carcinoma by necrosis or increased mitotic activity [19-21]. Tumors that meet none of these criteria are classified as benign struma, even when cellular or proliferative [13]. Molecular testing for BRAF, RAS, and TERT alterations is particularly advantageous in borderline proliferative lesions or when treatment decisions, such as thyroidectomy or radioactive iodine, depend on the diagnosis, but its results are supportive rather than decisive [21,22].

The items that a pathology report for struma ovarii should document are summarized as a checklist in Table 4.

Item	What to document	References
Gross findings	Tumor size, laterality, capsule and surface integrity, rupture, adhesions	[1,2]
Composition	Proportion of thyroid tissue; other teratomatous elements	[1,2]
Histological patterns	Architectural and cytological patterns; proliferative or hyperplastic change reported as benign when criteria for carcinoma are absent	[12,13]
Carcinoma	Type (WHO thyroid terminology), size, stromal or vascular invasion, high-grade features	[1,19-21]
Strumal carcinoid	Presence and extent of a neuroendocrine component, with marker results	[9,16]
Extra-ovarian disease	Peritoneal, omental, or nodal deposits; HDFCO terminology when the thyroid tissue is bland	[7,8,20]
Ancillary studies	Immunohistochemistry; molecular results interpreted as adjuncts	[21,22]
Recommendations	Neck ultrasonography and serum thyroglobulin surveillance when carcinoma or HDFCO is diagnosed	[24-26]

TABLE 4: Reporting checklist for struma ovarii

WHO: World Health Organization; HDFCO: highly differentiated follicular carcinoma of ovarian origin.

Limitations

This review faces a number of constraints. Being a narrative review, there is a potential for bias in the selection of studies, and no aggregated estimates were derived. The majority of the data regarding struma-derived carcinoma, HDFCO, and molecular changes are drawn from small, retrospective series and case-based pooled analyses, which exhibit diverse histological classifications, treatments, and follow-up procedures [22,24-28]. For instance, a systematic review of HDFCO found only 20 patients, leading to the conclusion that the disease's rarity prevents definitive conclusions about the best treatment approach [29]. Additionally, the performance data for various immunohistochemical markers were inferred from research on other ovarian tumors [14,15,18], and the suggested algorithm is based on expert synthesis rather than prospective validation.

Conclusions

Struma ovarii is known for its ability to mimic other conditions, as its atypical patterns can resemble nearly all ovarian tumor types. When unexplained follicles, trabeculae, cysts, or oxyphil or clear cells are encountered, struma should be suspected and confirmed using thyroglobulin and TTF-1. The assessment of malignancy should rely on thyroid nuclear features, clear-cut invasion, or spread beyond the ovary, rather than just cellularity. Recent cohort studies indicate that carcinoma originating from struma typically has a very good prognosis, although it may recur after a long period, making precise histological classification important for risk-based management. Molecular insights into BRAF, RAS, and TERT provide a helpful, albeit tentative, tool for borderline cases.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Alka Yadav, Mithilesh Yadav

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